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<p>(21) International Application Number: PCT/GB99/03777 (22) International Filing Date: 12 November 1999 (12.11.99) (30) Priority Data: 60/108,410 13 November 1998 (13.11.98) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): GRIBBLE, Andrew, D. [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WITHERINGTON, Jason [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: MORPHOLINO-ETHOXYBENZOFURAN PROTEASE INHIBITORS</p> <div data-bbox="537 1131 1008 1329" data-label="Chemical-Block"> <p style="text-align: right;">(I)</p> </div> <p>(57) Abstract</p> <p>This invention relates to compounds of formula (I) wherein: n is 1 or 2; or a pharmaceutically acceptable salt thereof, which are inhibitors of cysteine proteases, particularly cathepsin K, and are useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor.</p>		

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MORPHOLINO-ETHOXYBENZOFURAN PROTEASE INHIBITORS

FIELD OF THE INVENTION

This invention relates to novel morpholinoethoxybenzofuran containing cyclic
5 alkoxyketone protease inhibitors, particularly inhibitors of cysteine and serine proteases,
more particularly compounds which inhibit cysteine proteases. The compounds of this
invention even more particularly relate to those compounds which inhibit cysteine proteases
of the papain superfamily, and particularly cysteine proteases of the cathepsin family. In
the most preferred embodiment, this invention relates to compounds which inhibit cathepsin
10 K. Such compounds are particularly useful for treating diseases in which cysteine proteases
are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis,
periodontitis, and arthritis.

BACKGROUND OF THE INVENTION

15 Cathepsin K is a member of the family of enzymes which are part of the papain
superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the
literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide
were disclosed in U.S. Patent No. 5,501,969 (called cathepsin O therein). Cathepsin K has
been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J. Biol.*
20 *Chem.* 271, 12517-12524; Drake, F.H., et al., (1996) *J. Biol. Chem.* 271, 12511-12516;
Bromme, D., et al., (1996) *J. Biol. Chem.* 271, 2126-2132.

Cathepsin K has been variously denoted as cathepsin O, cathepsin X or cathepsin
O2 in the literature. The designation cathepsin K is considered to be the more appropriate
one (name assigned by Nomenclature Committee of the International Union of
25 Biochemistry and Molecular Biology).

Cathepsins of the papain superfamily of cysteine proteases function in the normal
physiological process of protein degradation in animals, including humans, e.g., in the
degradation of connective tissue. However, elevated levels of these enzymes in the body
can result in pathological conditions leading to disease. Thus, cathepsins have been
30 implicated in various disease states, including but not limited to, infections by pneumocystis
carinii, trypanoma cruzi, trypanoma brucei brucei, and Crithidia fusciculata; as well as in
schistosomiasis malaria, tumor metastasis, metachromatic leukodystrophy, muscular
dystrophy, amyotrophy, and the like. See International Publication Number WO 94/04172,

published on March 3, 1994, and references cited therein. *See also* European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine proteases from P. gingivallis, called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design*, 2, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of

excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

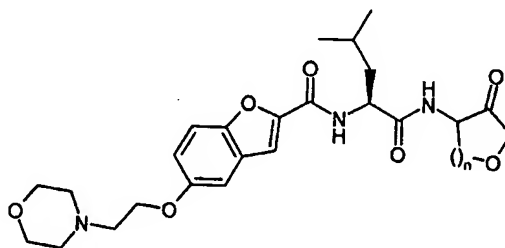
5 It now has been discovered that certain novel compounds are protease inhibitors, most particularly inhibitors of cathepsin K, and that these compounds are useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

10

SUMMARY OF THE INVENTION

An object of the present invention is to provide morpholinoethoxybenzofuran containing cyclic alkoxyketone protease inhibitors, particularly inhibitors of cysteine and serine proteases. In particular, the present invention relates to such compounds which
15 inhibit cysteine proteases, and particularly cysteine proteases of the papain superfamily. Preferably, this invention relates to such compounds which inhibit cysteine proteases of the cathepsin family and particularly, compounds which inhibit cathepsin K. The compounds of the present invention are useful for treating diseases, which may be therapeutically modified by altering the activity of such proteases.

20 Accordingly, in the first aspect, this invention provides a compound according to formula (I):



(I)

25 In another aspect, this invention provides a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.

In yet another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, such as cysteine and serine proteases. In particular, the method includes treating diseases by inhibiting cysteine proteases, and particularly cysteine proteases of the papain superfamily.

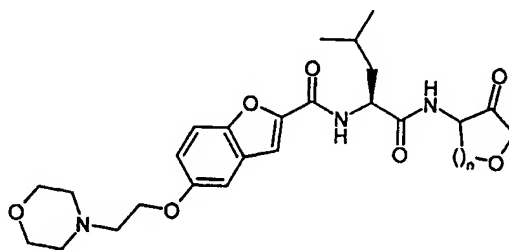
- 5 More particularly, the inhibition of cysteine proteases of the cathepsin family, such as cathepsin K is described.

- 10 In another aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula (I):

15



(I)

wherein:

- n is 1 or 2;
 20 or a pharmaceutically acceptable salt thereof.

- The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to formula (I) *in vivo*. Prodrugs of compounds of the present invention may be a prodrug of the ketone functionality of formula (I)
 25 compounds, specifically ketals or hemiketals.

If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and

diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

- 5 In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The preferred compounds of this invention are:

- 10 4-(*R,S*)-Amino-N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-tetrahydrofuran-3-one; and

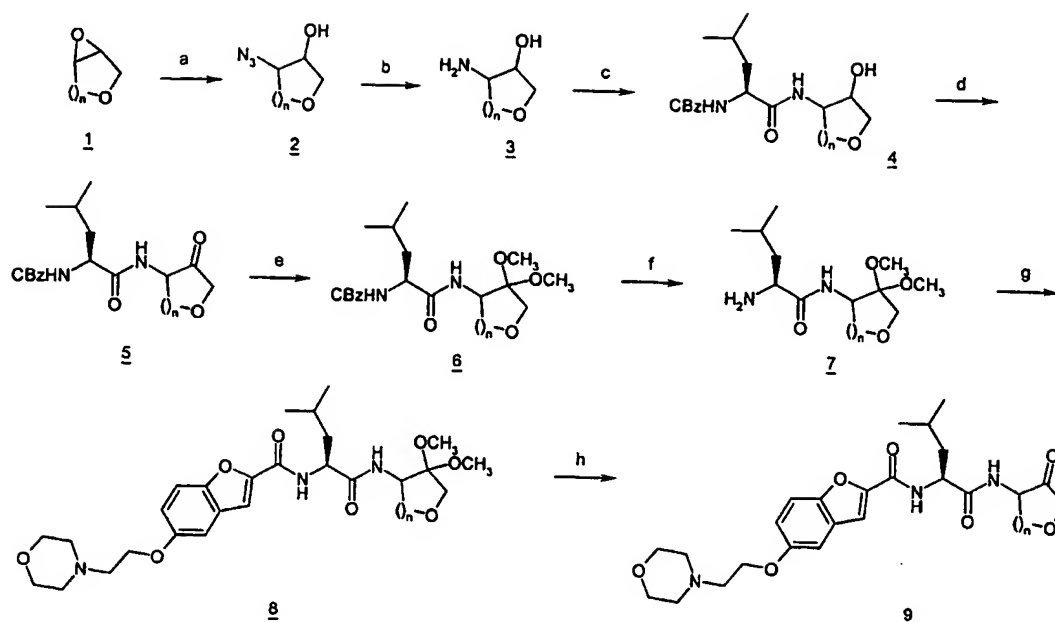
 4-(*R,S*)-Amino-N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-tetrahydropyran-3-one;

or a pharmaceutically acceptable salt thereof.

- 15 Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). "pTSA" means "*p*-toluenesulphonic acid". "TEMPO" means 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

- 20 Compounds of the formula (I) are generally prepared according to Scheme 1:

Scheme 1



- a) NaN_3 , MeOH; b) H_2 , Pd/C, EtOH; c) $(\text{CH}_3)_3\text{COCl}$, N-Cbz-L-Leu, CH_2Cl_2 ; d) Bleach, TEMPO, EtOAc/Toluene/ H_2O e) $(\text{MeO})_3\text{CH}$, pTSA; f) H_2 , Pd/C, MeOH then separate diastereomers; g) 5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl chloride, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 ; h) TFA, CH_2Cl_2

- 3,4-Epoxytetrahydrofuran or 3,4-epoxytetrahydropyran (1-Scheme-1) is added to a solution of sodium azide in aqueous methanol to provide the corresponding *trans*-4-azido-3-hydroxytetrahydrofuran or *trans*-4-azido-3-hydroxytetrahydropyran 2-Scheme-1, which is reduced over palladium on charcoal to give *trans*-4-amino-3-hydroxytetrahydrofuran or *trans*-4-amino-3-hydroxytetrahydropyran respectively 3-Scheme-1. 3-Scheme-1 is then reacted with trimethyl acetyl chloride and N-Cbz-L-leucine to provide the corresponding *trans*-4-(*R,S*)-amino-N-[(benzyloxycarbonyl)-*S*-leucine]-3-hydroxytetrahydrofuran or pyran (4-Scheme-1). Treatment of 4-Scheme-1 with bleach and TEMPO provides the corresponding 4-(*R,S*)-amino-N-[(benzyloxycarbonyl)-*S*-leucine]tetrahydrofuran-3-one or pyran-3-one (5-Scheme-1). Trimethylorthoformate addition to a solution of 5-Scheme-1 and *p*-toluenesulphonic acid yields the corresponding 4-(*R,S*)-amino-N-[(benzyloxycarbonyl)-*S*-leucine]-3,3-dimethoxytetrahydrofuran or pyran (6-Scheme-1), which upon reduction over palladium on charcoal gives the corresponding 4-

(*R,S*)-amino-*N*-(*S*-leucine)-3,3-dimethoxytetrahydrofuran or pyran (7-Scheme-1). Reaction of 7-Scheme-1 with 5-(2-*N*-morpholinoethoxy)-benzo[*b*]furan-2-ylcarbonyl chloride and diisopropylethylamine provides the corresponding 4-(*R,S*)-amino- *N*-[[5-(2-*N*-morpholinoethoxy)-benzo[*b*]furan-2-ylcarbonyl]-*S*-leucine]-3,3-dimethoxytetrahydrofuran or pyran (8-Scheme-1).

- 5 Treatment of 8-Scheme-1 with trifluoroacetic acid yields the corresponding 4-(*R,S*)-Amino- *N*-[[5-(2-*N*-morpholinoethoxy)-benzo[*b*]furan-2-ylcarbonyl]-*S*-leucine]-tetrahydrofuran-3-one or pyran-3-one (9-Scheme-1).

- 10 Separate *R* and *S* diastereomers of the inventive compounds may be prepared as described above, from the individual diastereomers of intermediate 7-scheme-1, which are separated by chromatography or other well-known techniques.

The starting materials used herein are commercially available or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

- 15 Coupling methods to form amide bonds herein are generally well-known in the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984, are generally
20 illustrative of the technique and are incorporated herein by reference.

- Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term "amino
25 protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

- Acid addition salts of the compounds of formula (I) are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as
30 hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic acid.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier, excipient or

diluent. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water, or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate.

Alternately, these compounds may be encapsulated, tableted, or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds of formula (I) are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin

family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

5 The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma
brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis,
metachromatic leukodystrophy, muscular dystrophy, amyotrophy; and especially diseases in
which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage
loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis,
10 more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of
malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

15 The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain
superfamily, yet more particularly cysteine proteases of the cathepsin family, which
methods comprise administering to an animal, particularly a mammal, most particularly a
20 human in need thereof a compound of the present invention. The present invention
especially provides methods of treatment of diseases caused by pathological levels of
cathepsin K, which methods comprise administering to an animal, particularly a mammal,
most particularly a human in need thereof, an inhibitor of cathepsin K, including a
compound of the present invention. The present invention particularly provides methods for
25 treating diseases in which cysteine proteases are implicated, including infections by
pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well
as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular
dystrophy, amyotrophy, and especially diseases in which cathepsin K is implicated, most
particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival
30 disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and
rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone
disease.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to a patient of an effective amount of a compound of formula (I), alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

In accordance with this invention, an effective amount of one or more compounds of formula (I) is administered to inhibit the protease implicated in a particular condition or disease. Of course, this dosage amount will further be modified according to the type of administration of the compound. For example, "effective amount" for acute therapy, parenteral administration of a compound of formula (I) is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

Prodrugs of compounds of the present invention may be prepared by any suitable method. For those compounds in which the prodrug moiety is a ketone functionality, specifically ketals and/or hemiacetals, the conversion may be effected in accordance with conventional methods.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The compounds of this invention may be tested in one of several biological assays to determine the concentration of a compound which is required to have a given
5 pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic
10 peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 μ M final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments
15 found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

20 Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data
25 analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemistsry*, 1989, 28, 140):

$$v = V_m A / [K_a(1 + I/K_{i, app}) + A] \quad (1)$$

30

where v is the velocity of the reaction with maximal velocity V_m , A is the concentration of substrate with Michaelis constant of K_a , and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$5 \quad [AMC] = v_{ss} t + (v_0 - v_{ss}) [1 - \exp(-k_{obs}t)] / k_{obs} \quad (2)$$

where [AMC] is the concentration of product formed over time t , v_0 is the initial reaction velocity, and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant
 10 $(k_{obs} / \text{inhibitor concentration or } k_{obs} / [I])$ describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1988, 61, 201).

One skilled in the art would consider any compound with a K_i of less than 50 micromolar to be a potential lead compound. Preferably, the compounds used in the
 15 method of the present invention have a K_i value of less than 1 micromolar. Most preferably, said compounds have a K_i value of less than 100 nanomolar.

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by
 20 centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 minutes on ice. The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear
 25 cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

30 The beads were mixed with the cells and the suspension was incubated for 30 minutes on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to

dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to $1.5 \times 10^4/\text{mL}$ in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 μM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 $\mu\text{g/mL}$) and an isotype control (IgG2a diluted to 100 $\mu\text{g/mL}$). The tubes were incubated at 37°C for 30 minutes.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 hours. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 hours. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 minutes, following which they were washed in water and incubated in buffer for 5 minutes at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 minutes at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

Examples

In the following synthetic examples, unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceeding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1Preparation of 4-(R,S)-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-S-leucine]-tetrahydrofuran-3-one5 a) *trans*-4-Azido-3-hydroxytetrahydrofuran

3,4-Epoxytetrahydrofuran (9 g, 105 mmol) was added to a stirred solution of sodium azide (27 g, 415 mmol) and ammonium chloride (9 g, 159 mmol) in aqueous methanol (95%, 200 ml). The reaction was heated to 75°C and stirred for 20 hours. The reaction was cooled, filtered and evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate, dried and evaporated under reduced pressure to afford the title compound as a colourless oil (10g, 74%).

¹H NMR δ (CDCl₃) 4.32 (m, 1H), 4.09 (dd, 1H, J = 4.8, 9.9 Hz), 3.99 (dd, 1H, J = 4.3, 10.1 Hz), 3.94 (m, 1H), 3.81 (dd, 1H, J = 2.1, 9.9 Hz), 3.73 (dd, 1H, J = 1.8, 10.1 Hz), 2.72 (d, 1H, J = 4.6 Hz).

15

b) *trans*-4-Amino-3-hydroxytetrahydrofuran hydrochloride

A mixture of *trans*-4-azido-3-hydroxytetrahydrofuran (10 g, 77 mmol) and 10% palladium on charcoal (1g) in ethanol (150 ml) was stirred under an atmosphere of hydrogen (35 psi) for 12 hours. The mixture was filtered and treated with 100 ml of ethanolic HCl to afford, after evaporation under reduced pressure, the title compound as a brown solid (10.5g, 97%), m.p. 132 °C

¹H NMR δ (d₆ DMSO) 8.37 (s, 3H), 4.13 (m, 1H), 3.84 (dd, 1H, J = 4.9 and 14.3), 3.76 (dd, 1H, J = 5.5, 10.0 Hz), 3.58 (dd, 1H, J = 2.7, 10.0 Hz), 3.34 (m, 3 H).

20

c) *trans*-4-(R,S)-Amino-N-[(benzyloxycarbonyl)-S-leucine]-3-hydroxytetrahydrofuran

Trimethylacetyl chloride (6.88 ml) was added to a stirred solution of N-Cbz-L-leucine (16.19g, 61 mmol) in dichloromethane (360 ml). After 1 h, *trans*-4-amino-3-hydroxytetrahydrofuran. HCl (7.1g, 50.9 mmol) and triethylamine (14.2ml) in dichloromethane (140ml) was added and the mixture was allowed to stir overnight. The reaction mixture was poured into water and extracted with dichloromethane. The combined organic layers were washed with 1N HCl, saturated sodium hydrogen carbonate, brine and dried. Evaporation under reduced pressure afforded the title compound (11.5g, 44%).

30

¹H NMR δ (CDCl₃, 250 MHz) 7.4-7.3 (m, 6H), 6.7 (br d, 1H), 5.5 (dd, 1H), , 5.1-5.0 (m, 3H), 4.2-4.0 (m, 4H), 3.7-3.5 (m, 2H), 1.7-1.5 (m, 3H), 1.0 (dd, 6H).

MS calcd for (C₁₈H₂₆N₂O₅ + H)⁺: 351. Found: 351.

d) 4-(*R,S*)-Amino-N-[(benzyloxycarbonyl)-*S*-leucine]-tetrahydrofuran-3-one

A solution of bleach (400ml), containing sodium bicarbonate (28g), was added dropwise to a rapidly stirred mixture of *trans*-4-(*R,S*)-amino-N-[(benzyloxycarbonyl)-*S*-leucine]-3-hydroxytetrahydrofuran (11.5g, 32.85 mmol), sodium bromide (3.57g), TEMPO (50mg) in EtOAc (200ml), toluene (200ml) and water (30ml). After a persistent orange colour developed, a solution of potassium iodide (2.48g) in 10% aqueous KHSO₄ (400ml) was added. The organic layer was washed with a solution of sodium thiosulphate in sodium bicarbonate, then brine and dried (MgSO₄). Evaporation under reduced pressure and purification of the residue by column chromatography afforded the title compound (5.5g, 35%).

¹H NMR δ (CDCl₃) 7.31 (m, 5H), 5.71 (app dd, 1H, J = 8.4, 14.8 Hz), 5.06 (m, 2H), 4.50 (dd, 1H, J = 8.9, 18.0 Hz), 4.30-3.88 (m, 4H), 3.80 (app t, 1H, J = 9.6Hz), 1.64 (m, 3H), 0.91 (m, 6H).

MS calcd for (C₁₈H₂₄N₂O₅ + H)⁺: 349. Found: 349.

e) 4-(*R,S*)-Amino-N-[(benzyloxycarbonyl)-*S*-leucine]-3,3-dimethoxytetrahydrofuran

Trimethylorthoformate (4.2ml) was added slowly to a solution of 4-(*R,S*)-amino-N-[(benzyloxycarbonyl)-*S*-leucine]tetrahydropyran-3-one (4.4g, 12.6mmol) and *p*-toluenesulphonic acid (119mg) in methanol (20ml) at reflux for 45min. After removing the solvent under reduced pressure, the resulting oil was chromatographed on silica gel (ethyl acetate / hexane gradient) to give the title compound (4g, 80%)

¹H NMR δ (CDCl₃) 7.34 (s, 5H), 6.55 (d, 1H), 5.11 (m, 3H), 4.34 (q, 1H, J = 6.7Hz), 4.20 (m, 2H), 3.77 (s, 2H), 3.51 (m, 1H), 3.26 (d, 3H, J = 2.3Hz), 3.20 (d, 3H, J = 4.7Hz), 1.54 (m, 3H), 0.95 (s, 3H), 0.93 (s, 3H).

f) 4-(*R,S*)-Amino-N-(*S*-leucine)-3,3-dimethoxytetrahydrofuran

4-(*R,S*)-Amino-N-[(benzyloxycarbonyl)-*S*-leucine]-3,3-dimethoxytetrahydrofuran (5g, 12.7mmol) was subjected to hydrogenation at 50psi in methanol (200ml) containing 10% palladium on carbon (1g). After completion of the reaction, the mixture was filtered through celite and the solvent was removed under reduced pressure to afford the title compound (2.63g, 80%).

Chromatography on silica gel (CH₂Cl₂ containing MeOH, 0-4% gradient) allowed separation of the title compound into the two pure single diastereomers:

- diastereomer 1 (faster running) ^1H NMR δ (CDCl_3) 7.76 (d, 1H, $J = 7.3\text{Hz}$), 4.36 (dd, 1H, $J = 6.3$, 7.2Hz), 4.21 (dd, 1H, $J = 6.4$, 9.0Hz), 3.80 (s, 2H), 3.57 (dd, 1H, $J = 5.3$, 9.1Hz), 3.41 (dd, 1H, $J = 3.8$, 10.1Hz), 3.30 (s, 3H), 3.24 (s, 3H), 1.73 (m, 2H), 1.35 (m, 1H), 0.96 (d, 3H, $J = 6.7\text{Hz}$), 0.94 (d, 3H, $J = 6.6\text{Hz}$)
- 5 diastereomer 2 (slower running) ^1H NMR δ (CDCl_3) 7.77 (d, 1H, $J = 7.1\text{Hz}$), 4.36 (dd, 1H, $J = 6.4$, 12.9Hz), 4.21 (dd, 1H, $J = 6.5$, 9.1Hz), 3.80 (s, 2H), 3.55 (dd, 1H, $J = 5.3$, 9.0), 3.38 (dd, 1H, $J = 4.0$, 10.0), 3.30 (s, 3H), 3.25 (s, 3H), 1.72 (m, 2H), 1.38 (m, 1H), 0.96 (d, 3H, $J = 6.7\text{Hz}$), 0.94 (d, 3H, $J = 6.8\text{Hz}$).
- 10 g) 4-(*R,S*)-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-3,3-dimethoxytetrahydrofuran
- 5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl chloride (ca 200mg) was added to a stirred solution of 4-(*R,S*)-amino-N-(*S*-leucine)-3,3-dimethoxytetrahydrofuran (200mg, 0.37mmol) and diisopropylethylamine (0.2ml) in dichloromethane (10ml). After 3
- 15 hours, the mixture was concentrated *in vacuo* and purified by chromatography on silica gel (CH_2Cl_2 containing MeOH 0-3% gradient) to afford the title compound (185mg, 94%).
- ^1H NMR δ (CDCl_3 , 400 MHz) 7.4-7.3 (m, 2H), 7.2-7.0 (m, 3H), 6.6 (d, 1H), 4.7 (dd, 1H), 4.4 (dd, 1H), 4.3 (dd, 1H), 4.2 (app t, 2H), 3.8-3.7 (m, 6H), 3.5 (dd, 1H), 3.3 (s, 3H), 3.2 (s, 3H), 2.8 (t, 2H), 2.6 (m, 4H), 1.8-1.6 (m, 4H), 1.0 (dd, 6H).
- 20 MS calcd for ($\text{C}_{27}\text{H}_{39}\text{N}_3\text{O}_8 + \text{H}$) $^+$: 534. Found: 534.
- h) 4-(*R,S*)-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-tetrahydrofuran-3-one
- Trifluoroacetic acid (1.5ml) was added to a stirred solution of 4-amino-N-[(5-(2-N-morpholinoethoxy)benzo[b]furan-2-ylcarbonyl)-*S*-leucine]-3,3-dimethoxytetrahydrofuran
- 25 (68mg) in dichloromethane (1.5ml). After 2 h the solution was diluted with toluene (3ml) and concentrated. This was taken up in dichloromethane, washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford the title compound (40mg) as its TFA salt.
- ^1H NMR δ (CDCl_3) 7.8 (d, 1H), 7.4 (d, 1H), 7.3-7.0 (m, 4H), 4.8-4.7 (m, 1H), 4.6 (m, 2H), 4.3-3.9 (m, 9H), 3.8-3.6 (m, 2H), 3.5-3.4 (m, 2H), 3.1 (brs, 2H), 1.8-1.7 (m, 3H), 1.0 (dd, 6H).
- 30 MS calcd for ($\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_7 + \text{H}$) $^+$: 488. Found: 488.
- $K_i = 0.47\text{nM}$.

Example 2

5 Preparation of 4-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-S-leucine]-tetrahydropyran-3-one, diastereomer 1

a) Separate diastereomers of 4-(*R,S*)-Amino-N-(*S*-leucine)-3,3-dimethoxytetrahydropyran

Following the procedures of Example 1(a)-1(f), but starting from 3,4-epoxytetrahydropyran instead of 3,4-epoxytetrahydrofuran, the individual diastereomers of the title compound were
10 obtained after chromatographic separation:

diastereomer 1: $^1\text{H NMR } \delta$ (CDCl_3) 7.75 (d, 1H, $J = 8.1\text{Hz}$), 4.17 (m, 1H), 3.58 (m, 3H), 3.41 (dd, 1H, $J = 3.5, 9.7\text{Hz}$), 3.28 (s, 3H), 3.24 (s, 3H), 1.92 (m, 1H), 1.71 (m, 4H), 1.30 (m, 1H), 0.97 (d, 3H, $J = 6.4\text{Hz}$), 0.94 (d, 3H, $J = 6.3\text{Hz}$).

diastereomer 2: $^1\text{H NMR } \delta$ (CDCl_3) 7.8 (s, 1H), 4.16 (m, 1H), 3.59 (m, 3H), 3.49 (m, 1H),
15 3.28 (s, 3H), 3.24 (s, 3H), 1.92 (m, 1H), 1.72 (m, 4H), 1.41 (m, 1H), 0.97 (d, 3H, $J = 6.1\text{Hz}$), 0.95 (d, 3H, $J = 6.0\text{Hz}$).

b) 4-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-3,3-dimethoxytetrahydropyran, diastereomer 1
20 5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl chloride (0.065g, 0.2mmol) was added to a stirred solution of 4-amino-N-(*S*-leucine)-3,3-dimethoxytetrahydropyran, diastereomer 1 (0.05g, 0.18mmol) and diisopropylethylamine (0.12ml) in dichloromethane (5ml). After 45 minutes, the mixture was concentrated *in vacuo* and purified by chromatography on silica gel (CH_2Cl_2 containing MeOH 0-5% gradient) to afford the title
25 compound (0.100g, 89%) as a white solid.

$^1\text{H NMR } \delta$ (CDCl_3) 7.4 (app t, 2H), 7.2-7.1 (m, 2H), 6.9 (d, 1H), 6.5 (d, 1H), 4.6 (dd, 1H), 4.3-4.2 (m, 1H), 4.2-4.1 (m, 2H), 3.9-3.6 (m, 7H), 3.4 (d, 1H), 3.3 (s, 3H), 3.2 (s, 3H), 2.8 (t, 2H), 2.6 (dd, 4H), 2.00-1.7 (m, 5H), 1.0 (dd, 6H).

MS calcd for $(\text{C}_{28}\text{H}_{41}\text{N}_3\text{O}_8 - \text{H})^+$: 546. Found: 546.

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c) 4-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-S-leucine]-tetrahydropyran-3-one, diastereomer 1

- Trifluoroacetic acid (1ml) was added to a stirred solution of 4-amino-N-[[5-(2-N-morpholino-ethoxy)-benzo[b]furan-2-ylcarbonyl]-S-leucine]-3,3-dimethoxytetrahydropyran, diastereomer 1 (0.065g, 2mmol) in dichloromethane (1ml). After 1 h the solution was diluted with toluene (3ml) and concentrated *in vacuo* to afford the title compound (30mg, 100%) as a yellow solid.
- ¹H NMR δ (CDCl₃) 7.4 (m, 1H), 7.3-6.9 (m, 5H), 4.8-4.6 (m, 2H), 4.4 (m, 2H), 4.2-3.8 (m, 11H), 3.6 (dd, 2H), 3.2 (m, 2H), 2.7 (m, 1H), 2.1-1.9 (m, 1H), 1.8-1.7 (m, 2H), 1.0 (dd, 6H).
- MS calcd for (C₂₆H₃₅N₃O₇ - H)⁺: 502. Found: 502.
- K_i = 2.5nM.
- Pit assay: IC₅₀ = 130nM.

Example 3

15

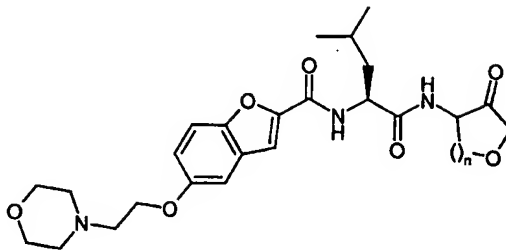
Preparation of 4-Amino- N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-S-leucine]-tetrahydropyran-3-one, diastereomer 2

- By analogous procedures to those described in Example 2(b)-2(c), but using diastereomer 2 of 4-amino-N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-S-leucine]-3,3-dimethoxytetrahydropyran (Example 2(a)), the title compound was obtained.
- ¹H NMR δ (CDCl₃) 7.5-6.9 (m, 6H), 5.0-4.8 (m, 2H), 4.4 (dd, 2H), 4.2-3.9 (m, 4H), 3.8 (brs, 2H), 3.6 (brs, 2H), 3.1 (brs, 2H), 2.8-2.7 (m, 1H), 2.0-1.8 (m, 1H), 1.8-1.6 (m, 3H), 1.0-0.9 (m, 6H).
- MS calcd for (C₂₆H₃₅N₃O₇ - H)⁺: 502. Found: 502.
- K_i = 2.3nM.
- Pit Assay: IC₅₀ = 50nM

- The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I):



(I)

wherein:

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein n is 1.

3. A compound according to claim 1 wherein n is 2.

4. A compound according to claim 3 selected from the group consisting of:
 4-(*R*)-Amino-N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-tetrahydropyran-3-one; and
 4-(*S*)-Amino-N-[[5-(2-N-morpholinoethoxy)-benzo[b]furan-2-ylcarbonyl]-*S*-leucine]-tetrahydropyran-3-one.

5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier, excipient or diluent.

6. A method of inhibiting a cysteine protease which comprises administering to a patient in need thereof an effective amount of a compound according to claim 1.

7. A method according to claim 6 wherein the cysteine protease is cathepsin K.
8. A method of inhibiting bone loss which comprises administering to a patient in need thereof an effective amount of a compound according to claim 1.
9. A method of treating osteoporosis which comprises administering to a patient in need thereof an effective amount of a compound according to claim 1.
10. A method of treating gingival or periodontal disease which comprises administering a patient in need thereof an effective amount of a compound according to claim 1.
11. A method of treating a disease characterized by excessive cartilage or matrix degradation which comprises administering to a patient in need thereof an effective amount of a compound according to claim 1.
12. A method according to claim 11 wherein said disease is osteoarthritis or rheumatoid arthritis.
13. A compound according to any one of claims 1 to 4 for use as a medicament.
14. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases by inhibition of a cysteine protease.
15. The use of a compound according to claim 14 wherein the cysteine protease is cathepsin K.
16. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of bone loss.

17. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of osteoporosis.

18. The use of a compound of the formula (I) as defined in claim 1 in the
5 manufacture of a medicament for the treatment of gingival or periodontal disease.

19. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases characterized by excessive cartilage or matrix degradation.

10

20. The use of a compound according to claim 19 wherein the disease is osteoarthritis or rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03777

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 A61K31/343 A61K31/365 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 59526 A (DESJARLAIS RENEE LOUISE ;SMITHKLINE BEECHAM CORP (US); YAMASHITA D) 25 November 1999 (1999-11-25) the whole document	1-20
P, X	WO 99 53039 A (SMITHKLINE BEECHAM CORP ;TOMASZEK THADDEUS ANTHONY (US); TEW DAVID) 21 October 1999 (1999-10-21) the whole document	1-20
Y	WO 98 50533 A (FENWICK ASHLEY EDWARD ;GRIBBLE ANDREW D (GB); SMITHKLINE BEECHAM P) 12 November 1998 (1998-11-12) the whole document	1-20
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

3 April 2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03777

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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